COMMENTARY

Towards personalized medicine: Unlocking on-demand organ manufacturing through 3D bioprinting

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Currently, organ transplantation is the only effective treatment for organ failure, but it faces a severe shortage of available organs, with a supply-demand ratio of 1:15, and long-term immune rejection. Additionally, disease research and drug development rely heavily on two-dimensional cell models and animal models, resulting in lengthy development cycles (over 10 years), high costs ($1-3 billion), and high failure rates (up to 90%). This underscores the urgent need for organs that accurately mimic human physiological and pathological states for both transplantation and medical research. However, the on-demand manufacturing of human organs remains a significant challenge in the medical and engineering fields.

3D bioprinting, which precisely assembles living cells and biomaterials, holds great potential for constructing complex tissues and organs. Recent advances in 3D bioprinting and stem cell technologies have led to significant breakthroughs in organ manufacturing. In 2019, Adam Feinberg et al. printed a miniaturized heart chamber model that could beat synchronously for weeks,[1] marking a significant milestone in biofabrication. Xenotransplantation has also advanced with gene-editing technologies. In 2022, the first gene-edited pig heart was transplanted into a patient with heart failure, extending his life by 60 days.[2] In 2023, a gene-edited pig kidney functioned normally in a brain-dead human for 61 days, showcasing significant potential for clinical

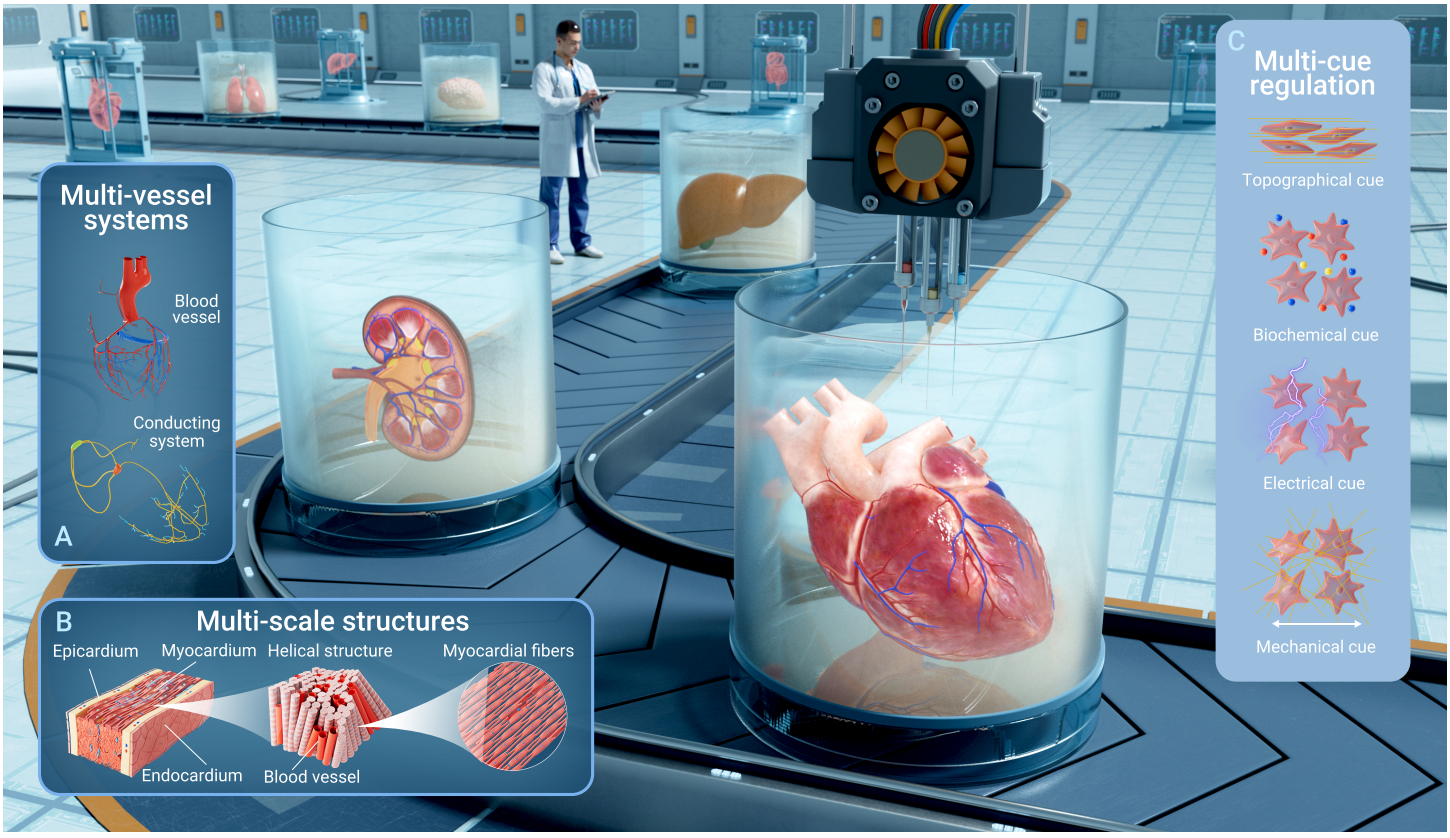

Figure 1. Schematic diagram of on-demand manufacturing pipeline of human organs (A) Essential vessel systems for human organs, such as blood vessels and conducting systems. (B) Representative multiscale structures of the heart. (C) Diverse biochemical and biophysical cues that regulate human organ functions.

applications.

Despite recent advances, xenotransplantation (e.g., gene-edited pig organs) still faces significant challenges, such as immune rejection, cross-species viral infections, and ethical concerns, limiting its potential as a future clinical treatment. In contrast, in vitro manufactured organs using patient-specific cells circumvent genetic differences and ethical issues, making them more acceptable to patients. These artificial organs can be tailored in physical structure, cell composition, and specific genes, making them ideal models for studying the effects of environmental factors, drugs, and genetics on organ function. They provide an excellent platform for human disease research and drug development. In late December 2022, the United States formally approved the FDA Modernization Act 2.0, eliminating outdated requirements for animal testing in new drug research and development. This legislative change removes institutional barriers, paving the way for the advancement and application of in vitro organ manufacturing. Organ manufacturing entails intricate biological, physical, and chemical processes, each with numerous constraints. Despite significant advancements in 3D bioprinting, we have yet to achieve the manufacturing of in vitro organs that closely emulate physiological biomimicry, incorporating diverse heterogeneous components, multi-scale structures, and dynamic functionality.

Human organs exhibit a high degree of heterogeneity and dynamic changes in their cellular and material components. For instance, single-cell sequencing has identified nine major cell types and over 32 subtypes within the human heart. Moreover, different regions of the heart (i.e., spatial domain) and various developmental stages (i.e., temporal domain) display unique cell types and proportions, with the extracellular matrix adapting to maintain the heart's structural and functional balance. Replicating the intricate morphology and cellular attributes of human organ development solely through 3D bioprinting technology remains impractical. A promising strategy involves integrating 3D bioprinting with stem cell technology and utilizing advanced cell programming techniques, such as CRISPR/Cas9 and transcription factors, to modulate the developmental fate of various cell lineages in one pot. Moreover, the development of cell-instructive biomaterials and dynamic hydrogels is crucial for effectively modulating cellular responses and enhancing tissue functionality, thereby ensuring the seamless integration of various organ systems.

The survival of most human organs hinges on a robust vascular network. For the heart, the non-proliferative nature of the myocardium and its high cell density require the development of an intricate vascular network to supply oxygen and nutrients. While current 3D bioprinting can fabricate vascular networks with diameters larger than hundreds of micrometers,[3] finer vessels typically form through endothelial self-assembly. The rapid construction and seamless integration of multiscale vascular networks within complex organ structures present a significant challenge. In addition to complex vascular networks, the development of functional native organs necessitates the incorporation of additional systems, including the neural system for nerve innervation and the lymphatic system for immune regulation. For optimal cardiac function, it is also imperative to establish an electrical conduction system to ensure the synchronized and coordinated contraction of the heart's multiple chambers.

Human organs possess multi-scale structures that create essential microenvironments and provide mechanical support crucial for cell growth and functional development. For example, the heart is composed of myocardial fibers arranged in a helical pattern across the ventricular walls, significantly enhancing its pumping efficiency.[4] Replicating this complex macro- and micro-scale architecture in vitro poses a significant challenge, necessitating the development of novel formation mechanisms and bioprinting strategies for cell-laden biomaterials by leveraging physical fields and chemical regulation. The conflicting demands of rapid printing speeds and high resolution are critical for organ manufacturing, ensuring both printing fidelity and cell viability. Achieving this may be possible through high-throughput, multi-nozzle parallel printing strategies or multi-scale 3D bioprinting strategies with adjustable resolution that simultaneously match micro- and macro-structures.[5]

The in vivo development of human organs is governed by a myriad of biological, chemical, and physical cues. For the heart, factors such as fluid shear stress, blood flow-induced stretching forces, and bioelectrical signals play pivotal roles in shaping functional maturity. Unraveling the regulatory mechanisms of these diverse signals and their coordination with organ development poses significant challenges. A promising approach involves the development of advanced bioreactors capable of accurately replicating and modulating these signals in vitro at various developmental stages, which is essential for facilitating the functional maturation of 3D-printed organs. Additionally, producing clinical-sized organs for transplantation requires billions of cells, necessitating the development of more efficient and cost-effective cell differentiation and storage technologies. Balancing personalized design of 3D bioprinted organs with scalable manufacturing requires a transition from trial-and-error approaches to automated, standardized, and intelligent printing processes. The integration of artificial intelligence for design and process control, coupled with multi-sensor real-time monitoring and correction, holds promise for enhancing both the quality and efficiency of organ printing.

Beyond its applications in organ transplantation, organ manufacturing holds the potential to develop in vitro multi-organ interconnected systems for disease modeling and drug screening. However, achieving such multi-organ interconnections poses significant challenges, including the integration of diverse tissue types, the synchronization of physiological functions, and the maintenance of homeostasis within a confined environment. A promising approach to address these challenges involves combining 3D bioprinting with organ-on-a-chip technology to accurately replicate the intricate structures, as well as the physical and biochemical conditions of specific organs. Incorporating multi-sensors to monitor physiological parameters—such as temperature, pH, and oxygen levels—along with adaptive feedback mechanisms, can enable dynamic adjustments to maintain organ synchronization. Additionally, leveraging artificial intelligence and machine learning algorithms to analyze data from these multi-organ systems can optimize organ performance and enhance their overall synchronization.

3D bioprinting is garnering increasing attention as a cutting-edge technology in the biomedical field. Although current 3D-printed organs are still in their infancy and face significant limitations, these challenges will be gradually overcome through technological advancements and multidisciplinary collaboration. Future advancements in the on-demand manufacturing of human organs that closely replicate both anatomical and functional characteristics will require innovations in advanced biomaterials, precise stem cell regulation, and upgraded 3D bioprinting technologies. We anticipate that 3D bioprinted organs will ultimately provide viable alternatives for organ transplantation and revolutionize our understanding of complex diseases, as well as the development of novel drugs and therapies.

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DECLARATION OF INTERESTS

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ETHICAL STATEMENT AND PATIENT CONSENT

Not applicable.